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CASE REPORT
Treatment of a lower urinary tract infection in a cat caused by a multi-drug methicillin-resistant *Staphylococcus pseudintermedius* and *Enterococcus faecalis*

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Staphylococci and enterococci are common causes of urinary tract infections in cats. However, both species are rarely implicated together as causes of lower urinary tract infections associated with urethral obstruction. This report describes the first case of a multi-drug methicillin-resistant *Staphylococcus pseudintermedius* belonging to *spa* type t06 and *Enterococcus faecalis* urinary infection in a cat with pre-existing and recurrent urethral obstruction. Both species were isolated at $>10^5$ CFU/ml from a cystocentesis urine specimen. Clinical and ultrasound features, results from urinalysis, urine culture, molecular typing and susceptibility testing by minimal inhibitory concentrations determination are described. Oral treatment with nitrofurantoin, the only antimicrobial agent that constituted a viable therapeutic option, had a positive outcome.

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A 5-year-old, neutered male Persian cat, living in an apartment was presented with urethral obstruction. The cat was fed a commercial dry cat food. The owner reported a 4-day history of inappetence, reduced water intake, dysuria, stranguria and constipation and generalised weakness. On physical examination, its bladder was enlarged and painful and the cat appeared depressed. Blood samples were taken for routine laboratory evaluation. The complete blood count revealed mild leukocytosis ($20.5 \times 10^3/\mu l$, reference interval (RI) $3.8–19 \times 10^3/\mu l$) with neutrophilia (18,655/μl, RI 1290–15,950/μl) and all red blood cell parameters were within reference range. Serum biochemical analysis revealed severe azotaemia (blood urea nitrogen, >300 mg/dl, RI 10–30 mg/dl; creatinine >10 mg/dl, RI 0.8–2.0 mg/dl) and hyperkalaemia (potassium 9.6 mmol/l, RI 3.5–5.1 mmol/l). Tests for feline leukaemia virus and feline immunodeficiency virus were negative (Snap Combo FeLV Ag/FIV Ab Test Kit, Idexx Labs). The cat was treated with diazepam (Diazepam; Intervet, 0.2 mg/kg IV) and butorphanol (Torbugesic, Fort Dodge) at the dosage of 0.4 mg/kg and a sterile catheter was passed through the urethra to the bladder, and then sutured to the perineal skin. Haemorrhagic urine was removed and analysed (see Table 1). Urinalysis revealed pH 7.0 and the absence of crystalluria. The cat was treated with intravenous physiological saline solution 0.9% to resolve the post-renal uraemia and hyperkalaemia, ranitidine (Zantac; GlaxoSmithKline, 2 mg/kg q12h IV) to reduce gastric acidity, and butorphanol (0.4 mg/kg q8h IM) ensured analgesia. On day 3, the urethral catheter was removed and the cat was seen to urinate on its own. Haematology and serum biochemistry parameters were within reference ranges. After catheterisation, an antimicrobial treatment course of amoxicillin combined with clavulanic acid (Synulox; Pfizer) at the dose of 12.5 mg/kg body weight, twice daily, for 1 week was instituted. The cat was discharged from the hospital with feline Urinary So diet. On day 15 the cat was re-evaluated for persistent haematuria, pollakiuria and stranguria due to a partial urethral obstruction. The urinalysis was compatible with inflammation in the absence of bacterial infection (Table 1). Abdominal ultrasound examination detected acoustic shadowing in the bladder consistent with cellular debris, but no calculi, mass, thickening

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Table 1. Urinalysis and urine culture results during treatment and follow-up.

Parameter and normal range	Day 1 (1st urethral obstruction)	Day 15	Day 23 (2nd urethral obstruction and LUTI)	Day 31 (5 days after the beginning of nitrofurantoin treatment, 8 days from LUTI diagnosis)	Day 46 (20 days after the beginning of nitrofurantoin treatment)	Day 51 (3rd urethral obstruction and urethrostomie/25 days after the beginning of nitrofurantoin treatment)	Day 86 (60 days after the beginning of nitrofurantoin treatment)
Specific gravity (1035–1060)	1037	1035	1015	1010	1030	1035	1020
pH (6–7)	7	7	7.5	8	6	7	6.5
Protein (0 to trace) mg/dl	300	>2000	300	Low	Negative	300	Negative
Glucose (negative)	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Bilirubin (negative)	Negative	Negative	Negative	Negative	Negative	Negative	Negative
RBC/HPF (<5)	>300	40–50	>300	rare	0–1	>300	1–2
WBC/HPF (<5)	0–1	0–1	8–10	0	1–2	2	0–1
Crystals (none)	None	None	None	None	None	None	None
Epithelial cells (occasional)	Rare	Rare	Occasional	Occasional	Rare	Rare	Rare
Bacteria (none if cystocentesis used)	None	None	Present	Present	None	None	None
Culture	Not available	Not available	*Staphylococcus pseudintermedius* ($>10^5$ CFU/ml) and *Enterococcus faecalis* ($>10^5$ CFU/ml)	Negative	Negative	Negative	Negative

RBC/HPF = red blood cell average count under high power field (400×); WBC/HPF = white blood cell average count under high power field (400×).

or mineralisation of the wall was observed. The left kidney had normal form, size and echogenicity. The right kidney had a cystic cortical lesion. The prescription diet was maintained and flavoxate hydrochloride was prescribed (50 mg PO q 12h) for urethral spasm control. On day 23 a second complete urethral obstruction occurred, this time with a urinalysis compatible with lower urinary tract infection (LUTI). Urine culture was performed with a sample obtained by cystocentesis. A mixed LUTI was found caused by *Staphylococcus pseudintermedius* ($>10^5$ CFU/ml) and *Enterococcus faecalis* ($>10^5$ CFU/ml) isolates. Antimicrobial susceptibility testing was performed using the microbroth dilution method (DADE Behring Microscan PM21, USA), and interpreted according to CLSI guidelines M31-A3 and M100-S17[1,2] (Table 2). Discrimination between *S pseudintermedius* and *Staphylococcus intermedius* was undertaken by *pta* polymerase chain reaction-restriction fragment length polymorphism analysis.[3] Methicillin resistance in *S pseudintermedius* was confirmed by polymerase chain reaction detection of *mecA* (http://www.crl-ar.eu). The methicillin-resistant *S. pseudintermedius* (MRSP) harbored a SCC*mec* V cassette using MPCR1 and MPCR2 described by Kondo et al,[4] was Panton-Valentine leukocidin (PVL) negative,[5] and had *spa* type t06 (repeat sequence r01r02r03r03r06r05).[6]

Possible therapeutic options were based on the following principles: (i) both strains had to be susceptible to the antimicrobial agent; (ii) the agent had to have good pharmacodynamic and pharmacokinetic characteristics for use in LUTI; (iii) the antimicrobial agent could not be one of the critically important antimicrobials for human medicine.[7] Nitrofurantoin was the only antimicrobial to fit all three criteria (Table 2), and was prescribed at 4 mg/kg, q 8h, for 60 days (one quarter of the content of a 100 mg capsule was administrated PO after dilution in 5 ml of water with a syringe). The motivated owners of the cat were a veterinary student and her mother. This ensured compliance. There were clear signs of clinical improvement after 5 days and further urine samples collected on days 5, 20, 25 and 60 after commencing nitrofurantoin treatment were culture negative (Table 1). However, on day 51 after the first episode of urethral obstruction, a third episode of total obstruction occurred (Table 1), and was not related to the LUTI but probably due to the underlying presence of a feline idiopathic cystitis obstructive form. This required a perineal urethrostomy to alleviate the obstruction.

Obstructive idiopathic cystitis (OIC) constitutes a common medical problem of the lower urinary tract in male cats and Persian cats appear to be predisposed.[8,9] Urethral obstruction in cats may be present with a concurrent urinary tract infection at the time of obstruction relief.[9] Risk factors for the occurrence of a LUTI secondary to OIC remain to be elucidated. In a retrospective case–control study at three veterinary referral hospitals, significant risk factors for the acquisition of a methicillin-resistant *Staphylococcus aureus* infection compared to a methicillin-susceptible *S aureus* infection was the presence of a urinary catheter or co-infection.[10] The third consecutive urethral obstruction in our cat was associated with the presence of a mixed LUTI with a multi-drug resistant MRSP. In our case, repeated bladder over-distension and urinary catheterisation may have predisposed to LUTI. The lack of a closed collection system at the time of the urinary catheterisation and the use of antimicrobial therapy during and after the first catheterisation procedure could have been contributing risk factors for the LUTI. Antimicrobials and their selective pressure have already been implicated in companion animal MRSP infection or colonisation.[11] The systematic use of sterile closed collection systems attached to urethral catheters may overcome the occurrence of a LUTI secondary to OIC and result in antimicrobial prudent usage.

The recent clonal spread of MRSP in Europe is largely due to the emergence of a single clone (t02, ST71, SCC*mec* II–III).[6,12] *spa* type t06 and SCC*mec* V identical to those found in our MRSP, are associated with an MRSP clone currently circulating in North America (t06, ST68, SCCmec V).[6,13] In addition to β-lactam resistance, resistance in this isolate was observed to five antimicrobial classes; fluoroquinolones, lincosamides, macrolides, aminoglycosides and trimethoprim/sulfamethoxazole. Susceptibility was observed to tetracycline and chloramphenicol. This susceptibility pattern is also observed in the ST68 MRSP USA clone but not in the European one.[14] The MRSP causing LUTI in our patient is related to the ST68 clone which is a common cause of LUTI and pyoderma in the USA.

The *E. faecalis* also involved in the LUTI was ampicillin susceptible and exhibited low-level gentamicin resistance which is common in Portugal and in other European countries.[15,16] Therapeutic problems associated with enterococcal infections are often the result of intrinsic resistance of this genus towards cephalosporins, penicillinase-resistant penicillins, polymyxines, low concentrations of aminoglycosides, clindamycin, fluoroquinolones, streptogramines (*E. faecalis*) and trimethoprim/sulfamethoxazole.

This case report describes for the first time a co-infection with a multi-drug resistant MRSP and *E. faecalis* in a feline LUTI with pre-existing and recurrent urethral obstruction. In Switzerland, multi-drug resistant MRSP were previously found as a single causative pathogen in three cats with urinary tract infection.[17] The multi-resistance profile of MRSP strains spreading in Europe and North America typically includes resistance to all oral antimicrobials routinely used for treatment of infections in small animal medicine. In the present case report, therapeutic choices were even further narrowed by the co-infection. Nitrofurantoin usage is not authorised in animals. However, the rational for its use was the avoidance of using one of the critically important antimicrobials in human

Table 2. In vitro activity of 28 selected antimicrobial agents tested against uropathogenic bacterial strains and possible therapeutic options.

Antimicrobial agent	Uropathogenic bacterial strains							
	Methicillin-resistant *Staphylococcus pseudintermedius* (MRSP) (MIC, μg/ml)			*Enterococcus faecalis* (MIC, μg/ml)			Combined MRSP/*E. faecalis*	Possible therapeutic
		Clinical breakpoints			Clinical breakpoints		MIC interpretation	Options for UTI treatment
		Susceptible	Resistant		Susceptible	Resistant		
Amoxicillin-clavulanic acid	4/2	≤4/2	≥8/4	–	NA	NA	R	No
Ampicillin	>8	≤0.25	≥0.5	<0.25	≤8	≥16	R	No
Azithromycin	>4	≤2	≥8	–	NA	NA	R	NoA
Cefotaxime	<0.5	≤8	≥64	–	NA	NA	R	No
Chloramphenicol	8	≤8	≥32	8	≤8	≥32	S	NoA
Ciprofloxacin	>2	≤1	≥4	>2	≤1	≥4	R	No
Clindamycin	>2	≤0.5	≥4	–	NA	NA	R	NoA
Erythromycin	>4	≤0.5	≥8	>4	≤0.5	≥8	R	No
Fosfomycin	<32	≤32	>32	–	NA	NA	S	NoB
Fusidic acid	<2	≤2	≥32	–	NA	NA	S	NoB
Gatifloxacin	4	≤2	≥8	–	NA	NA	I	NoB
Gentamicin	>8	≤4	≥16	–	NA	NA	R	No
Gentamicin high level	–	NA	NA	<500	<500	≥500	S	NA
Levofloxacin	4	≤2	≥8	>4	≤2	≥8	R	NoB
Linezolid	2	≤4	>4	<1	≤2	≥8	S	NoB
Moxifloxacin	0.5	≤0.5	≥2	>2	≤1	≥2	R	NoB
Mupirocin	<4	≤4	≥256	–	NA	NA	S	NA
Netilmicin	8	≤8	≥32	–	NA	NA	S	NoB
Nitrofurantoin	<32	≤32	≥128	<32	≤32	≥128	S	Yes
Oxacillin*	>4	≤0.25	≥0.25	–	NA	NA	R	No
Penicillin	>8	≤0.12	≥0.25	2	≤8	≥16	R	No
Quinupristin-dalfopristin	<0.5	≤1	≥4	>2	≤1	≥4	R	NoB
Rifampin	<0.5	≤1	≥4	2	≤1	≥4	I	NoB
Streptomycin high level	–	NA	NA	<1000	<1000	≥1000	S	NoA
Teicoplanin	<1	≤8	≥32	<1	≤8	≥32	S	NoB
Tetracycline	<2	≤4	≥16	>8	≤4	≥16	R	No
Trimethoprim/sulfamethoxazole	>2/38	≤2/38	≥4/76	–	NA	NA	R	No
Vancomycin	2	≤2	≥16	2	≤4	≥32	S	NoB

NA = not applicable; No = therapy not possible due to antimicrobial resistance; NoA = therapy not applicable due to pharmacodynamic and pharmacokinetic antimicrobial agent characteristics; NoB = critically important antimicrobial agents for humans as categorised by the Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials Report.[5] Clinical breakpoint categorisation: S = susceptible bacterial isolate; I = intermediate bacterial isolate; R = resistant bacterial isolate. MIC = minimum inhibitory concentration.

*According to the new clinical breakpoints for *S. pseudintermedius*.[18]

medicine, eg, vancomycin. Infections with MRSP represent a real therapeutic challenge. The increased pressure to use last resort antimicrobials that are saved for the treatment of serious human infections raises important ethical questions that demand revision of regulatory and preventive measures to control this important animal health problem.

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